

Guillain-Barré syndrome following immunisation with *Haemophilus influenzae* type b conjugate vaccine

A. Gervaix, M. Cafilisch, S. Suter, Ch.-A. Haenggeli

Children's Hospital, University Hospital of Geneva, 30 bvd de la cluse, CH-1211 Genève 4, Switzerland

Received: 3 September 1992 / Accepted: 24 November 1992

Abstract. The Guillain-Barré syndrome (GBS) is an immune-mediated disease often associated with viral or bacterial infections and with immunisation. IgM antibodies have been implicated as the main trigger event in GBS. So far, only four cases of GBS have been observed following immunisation with a conjugate vaccine against *Haemophilus influenzae* type b. We report another patient with GBS after this vaccination. We measured immunoglobulins against the *H. influenzae* type b polysaccharide (PRP) component of the vaccine. Surprisingly the anti-PRP IgM antibody level was markedly elevated (100 µg/ml) in the plasma of this patient. We speculate that an excessive anti-PRP IgM antibody response to the vaccine might be the cause of GBS.

Key words: *Haemophilus influenzae* type b – Vaccination – Guillain-Barré syndrome

Introduction

The Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy, characterised by progressive symmetrical weakness. The maximal deficit develops over a few days or weeks, followed by a plateau phase of variable duration and gradual recovery.

Clinical diagnosis is confirmed by the presence of an albuminocytological dissociation in the CSF. Electrophysiological studies show proximal conduction block, reduced conduction velocities and prolonged distal latencies in 80% of patients with GBS [1]. Neuropathological findings consist of segmental demyelination and perivascular infiltration of mononuclear cells.

More than 50% of patients with GBS have a history of a preceding event such as a viral illness, an immunisa-

tion, or a surgical procedure. The only vaccine whose association with GBS has been confirmed is the swine flu vaccine used in the United States in 1976 and 1977 [2]. Four cases of GBS following vaccination with the *Haemophilus influenzae* type b diphtheria toxoid-conjugate vaccine (PRP-D, ProHiBiT) have been reported [3, 4].

We present another patient with GBS in close association with this vaccine.

Patient report

A 4-year 4-month-old girl was admitted with a 2-day history of unsteady gait and occasional falls. Ten days before the onset of the neurological symptoms she had received the *H. influenzae* type b conjugate vaccine (PRP-D, Prohibit). Neurological examination was normal except for decreased tendon reflexes in both lower extremities. Progressive weakness of the legs developed over the following days with hypotonia and complete loss of tendon reflexes. She complained of pain in her legs and feet and lost the ability to walk. On the 5th day, involvement of the lower cranial nerves with a monotonous voice, swallowing difficulties and bilateral facial weakness became evident.

CSF cell count was 1 mononuclear cell/mm³ and CSF protein was 0.89 g/l. Electrophysiological studies in the upper and lower extremities showed markedly decreased nerve conduction velocities of 14–26 ms (normal value 40–50 ms), and prolonged distal latencies of 10–29 ms (normal values < 6.5 ms).

Serological tests for cytomegalovirus, herpes, Epstein-Barr, *Borrelia burgdorferi* and *Campylobacter* were normal. Specific antibody levels to the capsular polyribosyl-ribitol-phosphate (PRP) of the *H. influenzae* type b vaccine are shown in Table 1.

The patient was treated with two 5-day courses of intravenous immunoglobulins (Sandoglobulin 0.4 g/kg/day) 2 weeks apart.

Following the first course of immunoglobulins cranial nerve function improved. Following the second course, muscle strength

Table 1. IgM and IgG antibodies to PRP in the plasma and the CSF 15 days after immunisation with PRP-D vaccine. Measurement of antibodies was performed using an ELISA

	Plasma	CSF
IgM (µg/ml)	100	0.0
IgG (µg/ml)	42	0.13

Correspondence to: A. Gervaix

Abbreviations: GBS = Guillain-Barré syndrome; PRP = polyribosyl-ribitol-phosphate

improved and she was able to walk with help. She was discharged 5 weeks after admission and had a normal neurological examination 4 weeks later, except for absent tendon reflexes.

Discussion

This is the fifth reported case of GBS following immunisation with *H. influenzae* type b vaccine. A causal relationship and the risk of GBS following *H. influenzae* type b vaccination have not been established. Eleven million doses of *H. influenzae* type b conjugate vaccine and 14 million doses of non-conjugate vaccines have been distributed in the United States as of June 1990 [4]. The estimated incidence of GBS in the general population is 2.4 per 100 000 person per year. It is only 0.8 in individuals less than 18 years of age [2]. Therefore, the rare cases of GBS following *H. influenzae* type b vaccination will not have any effect on the epidemiology of GBS. This, however, does not rule out a causal relationship between GBS and *H. influenzae* type b vaccination in the 4 reported cases and in our patient.

GBS is an immune-mediated disease improved by plasmapheresis and intravenous immunoglobulins [9]. The usually monophasic course of GBS suggests a primary immune response which does not persist. IgM antibodies have been implicated as the main trigger event in GBS [8]. Koski [6], using a highly sensitive C1 fixation and transfer assay, reported IgM antibodies in the serum of patients with GBS that reacted with peripheral nerve myelin and demonstrated the correlation of the kinetics of IgM antibody production and the clinical course of GBS. The neuropathies associated with paraproteinaemia have also been related to IgM antibodies [5]. It has therefore been postulated that in GBS, IgM antibodies elicited by T-cell-independent antigens such as glycolipids of viral and bacterial capsule might cross-react with glycoproteins of peripheral nerve myelin [8].

The component of the Hib capsule used as the targeted antigen in Hib vaccines is composed by a repetitive structure of carbohydrate (PRP) which elicits mainly a T-cell-independent response, with synthesis of IgM antibodies. The protein carrier used in conjugate vaccines (PRP-D) increases the production of IgM as well as IgG antibodies against PRP, elicits a T-dependent response and a booster response after re-immunisation. The anti-PRP IgM antibodies have been measured in several studies and were

2.0–13 µg/ml 1 month after immunisation with PRP-D vaccine [7].

In comparison, the anti-PRP IgM antibodies measured in the plasma of our patient were very high. IgM antibodies in the CSF were undetectable and the concentration of anti-PRP IgG antibodies low. We therefore postulate that an excessive amount of anti-PRP IgM antibodies produced in response to the PRP-D conjugate vaccine might be the cause of GBS. Unfortunately, anti-PRP antibodies have not been measured in the four patients reported so far. We have not repeated the measurement of anti-PRP antibodies in our patient because of the treatment with intravenous immunoglobulins which may contain IgG and IgM antibodies to PRP. We suggest that IgM antibodies be measured and cross-reaction to peripheral nerve myelin be studied in patients with GBS following immunisation with *H. influenzae* type b conjugate vaccine. This study could unfortunately not be performed in our patient.

References

- Asbury AK, Arnason BGW, Karp HR, McFarlin DE (1978) Criteria for diagnosis of Guillain-Barré syndrome. *Ann Neurol* 3:565–566
- Beghi E, Kurland LT, Mulder WD, Wiederholt WC (1985) Guillain-Barré syndrome: clinicopathologic features and effect of influenza vaccine. *Arch Neurol* 42:1053–1057
- D'Cruz ON, Shapiro ED, Spiegelman KN, et al (1989) Acute inflammatory demyelinating polyradiculopathy (Guillain-Barré syndrome) after immunization with *Haemophilus influenzae* type b conjugate vaccine. *J Pediatr* 115:743–746
- Gross TP, Hayes SW (1991) *Haemophilus conjugate vaccine* and Guillain-Barré syndrome. *J Pediatr* 118:161
- Ilyas AA, Willison HJ, Quarles RH, et al (1984) IgM in a human neuropathy related to paraproteinemia binds to a carbohydrate determinant in the myelin-associated glycoprotein and to a ganglioside. *Proc Natl Acad Sci USA* 81:1225–1229
- Koski CL (1990) Characterization of complement-fixing antibodies to peripheral nerve myelin in Guillain-Barré syndrome. *Ann Neurol* 27:544–547
- Lepow ML, Samuelsen JS, Gordon LK (1985) Safety and immunogenicity of *Haemophilus influenzae* type b polysaccharide diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. *J Pediatr* 106:185–189
- McFarlin DE (1990) Immunological parameters in Guillain-Barré syndrome. *Ann Neurol* 27:S25–S29
- Shahar E, Murphy G, Roifman CM (1990) Benefit of intravenously administered immune serum globulin in patients with Guillain-Barré syndrome. *J Pediatr* 116:141–144